IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	Application No. 10/596,209	*Confirmation No. 3439*
Filed:	June 2, 2006	
Applicants:	Nanping ZHONG et al.	This Amendment was electronically filed on July 6, 2009 using the USPTO's EFS-Web.
Title:	METHOD FOR THE ENANTIOMOERIC SEPARATION OF OPTICAL ACTIVE AMLODIPINE	
Art Unit:	1625	
Examiner:	Davis	
Attorney Docket:	8378/88501	
Customer No.:	22242	

Commissioner for Patents
P. O. Box 1450
Alexandria, Virginia 22313-1450

AMENDMENT A

Sir:

In response to the office action dated April 6, 2009, please amend this application as follows:

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 5 of this paper.

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

LISTING OF CLAIMS:

1. (currently amended) A method for preparing (S)-(-)-amlodipine comprising: ~~, comprises~~ dissolving racemic amlodipine and L-(+)-tartaric acid in an organic solvent containing 2-butanone to yield (S)-(-)-amlodipine-L-(+)-tartrate precipitate by reaction; separating the precipitate; recrystallizating the precipitate by using a lower alcohol solvent to obtain a solid; adding a lower alkyl halide into the solid; and neutralizing with ~~the resulting solution is neutralized by~~ an aqueous alkali to give (S)-(-)-amlodipine.

2. (Original) The method for preparing (S)-(-)-amlodipine according to claim 1, wherein said organic solvent is 2-butanone or mixture of 2-butanone with a cosolvent.

3. (Original) The method for preparing (S)-(-)-amlodipine according to claim 2, wherein said cosolvent is selected from the group consisting of methanol, ethanol, n-butanol, acetone, 2-pentanone, ethyl ether, methyl ethyl ether, ethyl acetate, ethyl formate, dichloromethane and chloroform.

4. (Original) The method for preparing (S)-(-)-amlodipine according to claim 1, wherein the molar ratio of racemic amlodipine to L-(+)-tartaric acid is 1:0.25~0.8.

5. (Original) The method for preparing (S)-(-)-amlodipine according to claim 4, wherein the molar ratio of racemic amlodipine to L-(+)-tartaric acid is 1:0.5.

6. (Original) The method for preparing (S)-(-)-amlodipine according to claim 1, wherein said lower alcohol solvent is selected from the group consisting of ethanol, methanol and isopropanol.

7. (currently amended) A method for preparing (R)-(+)-amlodipine comprising: ~~, comprises~~ dissolving racemic amlodipine and D-(-)-tartaric acid in an organic solvent containing 2-butanone to yield (R)-(+)-amlodipine-D-(-)-tartrate precipitate by reaction; separating the precipitate; recrystallizating the precipitate by using a lower alcohol solvent to obtain a solid; adding a lower alkyl halide into the solid; and neutralizing with ~~the resulting solution is neutralized by~~ an aqueous alkali to give (R)-(+)-amlodipine.

8. (Original) The method for preparing (R)-(+)-amlodipine according to claim 7, wherein said organic solvent is 2-butanone or mixture of 2-butanone with a cosolvent.

9. (Original) The method for preparing (R)-(+)-amlodipine according to claim 8, wherein said cosolvent is selected from the group consisting of methanol, ethanol, n-butanol, acetone, 2-pentanone, ethyl ether, methyl ethyl ether, ethyl acetate, ethyl formate, dichloromethane and chloroform.

10. (Original) The method for preparing (R)-(+)-amlodipine according to claim 7, wherein the molar ratio of racemic amlodipine to D-(-)-tartaric acid is 1:0.25~0.8.

11. (Original) The method for preparing (R)-(+)-amlodipine according to claim 10, wherein the molar ratio of racemic amlodipine to D-(-)-tartaric acid is 1:0.5.

12. (Original) The method for preparing (R)-(+)-amlodipine according to claim 7, wherein said lower alcohol solvent is selected from the group consisting of ethanol, methanol and isopropanol.

REMARKS

Claims 1-12 remain in this application.

Rejections under 35 USC 103

The presently claimed process actually is substantively different from the process of Dl at least in the following aspects.

1) D- or L-tartaric acid, (R,S)-amlodipine and DMSO form a DMSO-solvate precipitate in D1, i.e., DMSO is a part of the solvate precipitate (see Dl, especially the Examples), while D- or L-tartaric acid and (R,S)-amlodipine fonn a tartrate salt precipitate (not a solvate) in 2-butanone in the present invention. i.e.,2-butanone is not a part of the salt precipitate. Thus, DMSO is not only a solvent but also a reagent in D1, while 2-butanone is only a solvent in the present invention. Therefore, DMSO in the solvate precipitate may have to be removed by using other solvent, such as refluxing methanol in D1, while a solvent-free tartrate salt precipitate could be directly obtained by filtration in the present invention.

2) In addition, D-tartaric acid is used to obtain (S)-(-)-amlodipine (see D1, Examples 1-4) and L-tartaric acid is used obtain (R)-(+)-amlodipine (see Dl, Examples 5-8) in D1. On the contrary, L-tartaric is used to obtain (S)-(-)-amlodipine and D-tartaric is used to obtain (R)-(+)-amlodipine in the present invention. Thus, the reaction employed in D1 is different from the reaction of the present invention.

3) Dl discloses that the e.e. values of the obtained (S)-(-)-amlodipine and (R)-(+)-amlodipine are 98.4% and 98.5%, respectively (see Examples 3 and 8). In the present invention, the e.e. values of the obtained (S)-(-)-amlodipine and (R)-(+)-amlodipine are 99.0% and 98.8%, respectively (see Examples 1 and 2). Hence, the presently claimed process could reach higher e.e. value in comparison with Dl.

4) According to the material safety data sheets of DMSO and 2-butanone (see the attached documents), DMSO has a boiling point of 189°C and an explosion limits of 3.5-42% and 2-butanone has a boiling point of 79-80°C and an explosion limits of 1.8-10%, which means higher cost is needed to use and recover DMSO in view of safety and energy consumption in comparison with 2-butanone.

In view of the above discussion, D1 does not provide any teaching, suggestion or motivation to adopt the presently claimed process for producing enantiomers of amlodipine in industrial scale. D2 merely indicates that DMSO and 2-butanone are Class 3 solvents in view of their toxicity, but does not provide any information about using them in the separation of enantiomers of amlodipine. Hence, those skilled in the art would not obviously obtain the presently claimed process based on D1 and D2. Therefore, the pending claims 1-12 are non-obvious over Dl in view of D2 and Applicant respectfully requests allowance of those claims.

The Commissioner is hereby authorized to charge any additional fees which may be required with respect to this communication, or credit any overpayment, to Deposit Account No. 06-1135.

Respectfully submitted,

FITCH, EVEN, TABIN & FLANNERY

Dated: JUL 0 6 2009

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Electronic Acknowledgement Receipt

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Application Number:	10596209
International Application Number:	
Confirmation Number:	3439
Title of Invention:	Method for the enantiomoeric separation of optical active amlodipine
First Named Inventor/Applicant Name:	Nanping Zhong
Customer Number:	22242
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		88501_AmendmentA_07062009.pdf	194465 cb88b1a109599d4370e77c2cbdabd63158860a82	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	4
	Applicant Arguments/Remarks Made in an Amendment	5	6
Warnings:			
Information:			
	Total Files Size (in bytes):	194465	

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
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New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
10/596,209	06/02/2006	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 07/06/2009	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 12	Minus	** 20	= 0	X $ =		OR	X $52=	0
Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X $ =		OR	X $220=	0
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/JOSEPH BROOKS/